SECTION

II

DRUGS AFFECTING THE AUTONOMIC NERVOUS SYSTEM

9 General Organization and Functions of the Nervous System

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GENERAL ORGANIZATION AND FUNCTIONS OF THE NERVOUS SYSTEM

The nervous system is divided into two parts: the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS consists of the brain and spinal cord. The PNS consists of all *afferent* (sensory) neurons, which carry nerve impulses into the CNS from sensory end organs in peripheral tissues, and all *efferent* (motor) neurons, which carry nerve impulses from the CNS to effector cells in peripheral tissues. The peripheral efferent system is further divided into the *somatic nervous system* and the *autonomic nervous system*. The effector cells innervated by the somatic nervous system are skeletal muscle cells. The autonomic nervous system innervates three types of effector cells: (1) smooth muscle, (2) cardiac muscle, and (3) exocrine glands. While the somatic nervous system can function on a reflex basis, voluntary control of skeletal muscle is of primary importance. In contrast, in the autonomic nervous system voluntary control can be exerted, but reflex control is paramount.

Both somatic and autonomic effectors may be reflexly excited by nerve impulses arising from the same sensory end organs. For example, when the body is exposed to cold, heat loss is minimized by vasoconstriction of blood vessels in the skin and by the curling up of the body. At the same time, heat production is increased by an increase in skeletal muscle tone and shivering and by an increase in metabolism owing in part to secretion of epinephrine.

In general terms, the function of the autonomic nervous system is to maintain the constancy of the internal environment (*homeostasis*). This includes the regulation of the cardiovascular system, digestion, body temperature, metabolism, and the secretion of the exocrine glands.

ANATOMIC DIFFERENCES BETWEEN THE SOMATIC AND AUTONOMIC NERVOUS SYSTEMS

Anatomical differences between the peripheral somatic and autonomic nervous systems have led to their classification as separate divisions of the nervous system. These differences are shown in Figure 9.1. The axon of a somatic motor neuron leaves the CNS and travels without interruption to the innervated effector cell. In contrast, two neurons are required to connect the CNS and a visceral effector cell of the autonomic nervous system. The first neuron in this sequence is called the *preganglionic* neuron. The second neuron, whose cell body is within the ganglion, travels to the visceral effector cell; it is called the *postganglionic* neuron.

AUTONOMIC NERVOUS SYSTEM

The preganglionic neurons of the *sympathetic* nervous system have their cell bodies in the thoracic and lumbar regions of the spinal cord, termed the thoracolumbar division. The preganglionic neurons of the *parasympathetic* division have their cell bodies in the brainstem and in the sacral region of the spinal cord, termed the craniosacral division. The cranial part of the parasympathetic nervous system innervates structures in the head, neck, thorax, and abdomen (e.g., the stomach, part of the intestines, and pancreas). The cranial parasympathetic fibers leave the CNS in the oculomotor, facial, glos-

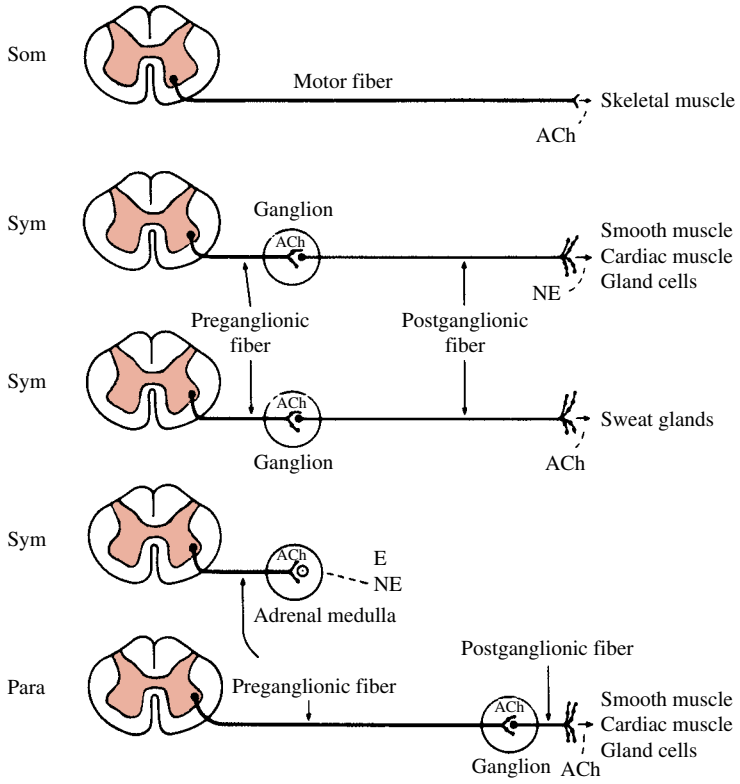

FIGURE 9.1
Anatomical characteristics and neurotransmitters of the somatic (Som), sympathetic (Sym), and parasympathetic (Para) divisions of the PNS. ACh, acetylcholine; E, epinephrine; NE, norepinephrine

sopharyngeal, and vagal cranial nerves. The sacral division of the parasympathetic nervous system innervates the remainder of the intestines and the pelvic viscera.

Location of the Autonomic Ganglia

The sympathetic ganglia consist of two chains of 22 segmentally arranged ganglia lateral to the vertebral column. The preganglionic fibers leave the spinal cord in adjacent ventral roots and enter neighboring ganglia, where they make synaptic connections with postganglionic neurons. Some preganglionic fibers pass through the vertebral ganglia without making synaptic connections and travel by way of splanchnic nerves to paired prevertebral ganglia in front of the vertebral column, where they make synaptic connections with postganglionic neurons. In addition, some sympathetic preganglionic fibers pass through the splanchnic nerves into the adrenal glands and make synaptic connections on the chromaffin cells of the adrenal medulla.

Because sympathetic ganglia lie close to the vertebral column, sympathetic preganglionic fibers are generally short. Postganglionic fibers are generally long, since they arise in vertebral ganglia and must travel to the innervated effector cells. There are exceptions to this generalization. A few sympathetic ganglia lie near the organs innervated (e.g., urinary bladder and rectum); thus, these preganglionic fibers are long and the postganglionic fibers are short. In contrast, the parasympathetic ganglia lie very close to or actually within the organs innervated by the parasympathetic postganglionic neurons.

Ratio of Preganglionic to Postganglionic Neurons

A single sympathetic preganglionic fiber branches a number of times after entering a ganglion and makes synaptic connection with a number of postganglionic neurons. Furthermore, some branches of this preganglionic fiber may ascend or descend to adjacent vertebral ganglia and terminate on an additional number of postganglionic neurons in these ganglia as well. Therefore, activity in a single sympathetic preganglionic neuron may result in the activation of a number of effector cells in widely separated regions of the body. Anatomically, *the sympathetic nervous system is designed to produce widespread physiological activity.* The sympathetic nervous system prepares the body for strenuous muscular activity, stress, and emergencies.

By contrast, parasympathetic preganglionic neurons are extremely limited in their distribution. In general, a single parasympathetic preganglionic fiber makes a synaptic connection with only one or two postganglionic neurons. For this reason, along with the fact that the ganglia are near or are embedded in the organs innervated, individual *parasympathetic preganglionic neurons influence only a small region of the body or affect only specific organs.* The parasympathetic nervous system is involved with the accumulation, storage, and preservation of body resources.

When the sympathetic integrative centers in the brain are activated (by anger, stress, or emergency), the body's resources are mobilized for combat or for flight. Stimulation of the sympathetic nervous system results in acceleration of the heart rate and an increase in the contractile force of the heart muscle. There is increased blood flow (*vasodilation*) through skeletal muscle and decreased blood flow (*vasoconstriction*) through the skin and visceral organs. Activity of the gastrointestinal tract, such as peristaltic and secretory activity, is decreased, and intestinal sphincters are contracted. The pupils are dilated. The increased breakdown of glycogen (*glycogenolysis*) in the liver produces an increase in blood sugar, while the breakdown of lipids (*lipolysis*) in adipose tissue produces an increase in blood fatty acids; these biochemical reactions make energy available for active tissues. In addition to generalized activation of the sympathetic system in response to stress, there can be more discrete homeostatic activation of the sympathetic system. For example, a selective reflex-associated alteration in the sympathetic outflow to the cardiovascular system can occur.

The parasympathetic system is designed to function more or less on an organ system basis, usually under conditions of minimal stress. For example, the activation of the gastrointestinal tract takes place during digestion of a meal; constriction of the pupil and accommodation for near vision are essential for reading.

AUTONOMIC NEUROTRANSMITTERS

Two PNS neurotransmitters, acetylcholine and norepinephrine, have particular clinical importance. Both are synthesized and stored primarily in the nerve terminals until released by a nerve impulse. It should be noted, to avoid confusion, that in the United States the transmitter in the sympathetic nervous system is referred to as *norepinephrine* and the major adrenal medullary hormone is referred to as *epinephrine.* In Europe and most of the world these two substances are called *noradrenaline* and *adrenaline,* respectively.

Neurotransmission in the PNS occurs at three major sites: (1) preganglionic synapses in both parasympathetic and sympathetic ganglia, (2) parasympathetic and sympathetic postganglionic neuroeffector junctions, and (3) all somatic motor end plates on skeletal muscle. Acetylcholine is the transmitter released at all of these sites except for the majority of sympathetic neuroeffector junctions. Neurons that release acetylcholine are called *cholinergic* neurons.

Norepinephrine is the transmitter released at most sympathetic postganglionic neuroeffector junctions. Neurons that release this substance are called *adrenergic* or *noradrenergic* neurons. Not all sympathetic postganglionic neurons are noradrenergic. The sympathetic postganglionic neurons that innervate the sweat glands and some of the blood vessels in skeletal muscle are cholinergic; that is, they release acetylcholine rather than norepinephrine, even though anatomically they are sympathetic neurons (Fig. 9.1).

Drugs that mimic the actions of acetylcholine are termed *cholinomimetic,* and those that mimic epinephrine and/or norepinephrine are *adrenomimetic.* The cholinomimetic drugs are also called parasympathomimetic drugs. The adrenomimetic drugs are often called sympathomimetic.

The receptors with which acetylcholine and other cholinomimetic drugs interact are called *cholinoreceptors,* while the receptors with which norepinephrine, epinephrine, or other adrenomimetic drugs combine are called *adrenoceptors.* It is common both in textbooks and the scientific literature to see these receptors referred to as cholinergic or adrenergic receptors. This is improper usage of the terms *cholinergic* and *adrenergic,* since these terms should be applied only to nerves.

Drugs that antagonize the actions of acetylcholine are known as *cholinoreceptor antagonists;* those that antagonize norepinephrine are known as *adrenoceptor antagonists.*

A number of other substances are released by sympathetic and parasympathetic neurons, often the same neurons that release norepinephrine or acetylcholine. These substances include adenosine triphosphate (ATP), neuropeptide Y, and substance P.

INNERVATION OF VARIOUS ORGANS BY THE SYMPATHETIC AND PARASYMPATHETIC NERVOUS SYSTEMS

Many visceral organs are innervated by both divisions of the autonomic nervous system. In most instances, when an organ receives dual innervation, the two systems work in opposition to one another. In some tissues and organs, the two innervations exert an opposing influence on the same effector cells (e.g., the sinoatrial node in the heart), while in other tissues opposing actions come about because different effector cells are activated (e.g., the circular and radial muscles in the iris).

Some organs are innervated by only one division of the autonomic nervous system.

Many neurons of both divisions of the autonomic nervous system are tonically active; that is, they are continually carrying some impulse traffic. The moment-to-moment activity of an organ such as the heart, which receives a dual innervation by sympathetic (noradrenergic) and parasympathetic (cholinergic) neurons, is controlled by the level of tonic activity of the two systems.

Blood Vessels

Most vascular smooth muscle is innervated solely by the sympathetic (noradrenergic) nervous system, but there are exceptions. Some blood vessels in the face, tongue, and urogenital tract (especially the penis) are innervated by parasympathetic (cholinergic) as well as sympathetic (noradrenergic) neurons. The parasympathetic innervation of blood vessels has only regional importance, for example, in salivary glands, where increased parasympathetic activity causes vasodilation that supports salivation.

The primary neural control of total peripheral resistance is through sympathetic nerves. The diameter of blood vessels is controlled by the tonic activity of noradrenergic neurons. There is a continuous outflow of noradrenergic impulses to the vascular smooth muscle, and therefore some degree of constant vascular constriction is maintained. An increase in impulse outflow causes further contraction of the smooth muscle, resulting in greater vasoconstriction. A decrease in impulse outflow permits the smooth muscle to relax, leading to vasodilation.

The Heart

The heart is innervated by both sympathetic and parasympathetic neurons; however, their distribution in the heart is quite different. Postganglionic noradrenergic fibers from the stellate and inferior cervical ganglia innervate the sinoatrial (S-A) node and myocardial tissues of the atria and ventricles. Activation of the sympathetic outflow to the heart results in an increase in rate (*positive chronotropic effect*), in force of contraction (*positive inotropic effect*), and in conductivity of the atrioventricular (A-V) conduction tissue (*positive dromotropic effect*).

The postganglionic cholinergic fibers of the parasympathetic nervous system terminate in the S-A node, atria, and A-V conduction tissue. Cholinergic fibers do not innervate the ventricular muscle to any significant degree. Activation of the parasympathetic outflow to the heart results in a decrease in rate (*negative chronotropic effect*) and prolongation of A-V conduction time (*negative dromotropic effect*). There is a decrease in the contractile force of the atria but little effect on ventricular contractile force.

The effect of a drug on the heart depends on the balance of sympathetic and parasympathetic activity at the time the drug is administered. An example is the effect of the ganglionic blocking agents (see Chapter 14), which nonselectively inhibit transmission in both sympathetic and parasympathetic ganglia. Normally, during rest or mild activity, the heart is predominantly under the influence of the vagal parasympathetic system. Blockade of the autonomic innervation of the heart by the administration of a ganglionic blocking agent accelerates the heart rate. Conversely, if sympathetic activity is dominant, as in exercise, ganglionic blockade will decrease the heart rate and also reduce ventricular contractility. Likewise, the magnitude of effect of a drug antagonist of sympathetic activity will depend upon how much sympathetic activity exists at the time it is given. A similar relationship exists between parasympathetic antagonists and the level of parasympathetic activity.

Cardiovascular Reflexes

Any sudden alteration in the mean arterial blood pressure tends to produce compensatory reflex changes in heart rate, contractility, and vascular tone, which will oppose the initial pressure change and restore the homeostatic balance. The primary sensory mechanisms that detect changes in the mean arterial blood pressure are stretch receptors (*baroreceptors*) in the carotid sinus and aortic arch.

The injection of a vasoconstrictor, which causes an increase in mean arterial blood pressure, results in activation of the baroreceptors and increased neural input to the cardiovascular centers in the medulla oblongata. The reflex compensation for the drug-induced hypertension includes an increase in parasympathetic nerve activity and a decrease in sympathetic nerve activity. This combined alteration in neural firing reduces cardiac rate and force and the tone of vascular smooth muscle. As a consequence of the altered neural control of both the heart and the blood vessels, the rise in blood pressure induced by the drug is opposed and blunted.

Injection of a drug that causes a fall in the mean arterial blood pressure triggers diametrically opposite reflex changes. There is decreased impulse traffic from the cardiac inhibitory center, stimulation of the cardiac accelerator center, and augmented vasomotor center activity. These changes in cardiac and vasomotor center activity accelerate the heart and increase sympathetic transmission to the vasculature; thus, the drug-induced fall in blood pressure is opposed and blunted.

The Eye

Two sets of smooth muscle in the iris control the diameter of the pupil. One set of muscles, which is arranged radially (dilator pupillae), is innervated by sympathetic (norad-

renergic) fibers that arise from cells in the superior cervical ganglion. Stimulation of them causes contraction of the radial smooth muscle cells, leading to dilation of the pupil (*mydriasis*). The other set of smooth muscle cells in the iris (constrictor pupillae) is circular and is innervated by parasympathetic neurons arising from cells in the ciliary ganglion. Stimulation of these cholinergic neurons causes contraction of the circular smooth muscle of the iris and constriction of the pupil (*miosis*).

The lens, which aids in visual accommodation, is attached at its lateral edge to the ciliary body by suspensory ligaments. When the smooth muscles of the ciliary body are relaxed, the ciliary body exerts tension on the lens, causing it to flatten. Thus, the eye is accommodated for far vision. Stimulation of parasympathetic cholinergic neurons, which arise in the ciliary ganglion, causes contraction of the smooth muscle of the ciliary body; this decreases the lateral tension on the lens. Naturally elastic, the lens thickens, and the eye accommodates for near vision. Drugs that block accommodation are called *cycloplegic*. Since the parasympathetic system is dominant in the eye, blockade of this system by atropine or of both autonomic systems by a ganglionic blocking agent will result in pupillary dilation and a loss of accommodative capacity.

Pulmonary Smooth Muscle

The bronchial tree is innervated by both divisions of the autonomic nervous system. Postganglionic parasympathetic neurons innervate bronchial smooth muscle directly and produce bronchoconstriction when stimulated. Sympathetic noradrenergic neurons appear to innervate vascular smooth muscle and parasympathetic ganglion cells. The effect of noradrenergic fibers on ganglion cells is to inhibit their firing. There is some controversy concerning the role of noradrenergic fibers in the regulation of airway smooth muscle tone. There is no doubt, however, that adrenoceptors are present on bronchial smooth muscle and that epinephrine from the adrenal gland and drugs such as epinephrine and isoproterenol produce bronchodilation of the airway.

Gastrointestinal Tract

The innervation of the gastrointestinal tract is complex. The myenteric and submucosal plexuses contain many interneurons. These possess a number of neurotransmitters and neuromodulators, including several peptides, such as enkephalins, substance P, and vasoactive intestinal peptide. Reflex activity within the plexuses regulates peristalsis and secretion locally. The effects of sympathetic and parasympathetic nerve stimulation are superimposed on this local neural regulation.

The myenteric and submucosal plexuses contain ganglion cells giving rise to excitatory cholinergic fibers that directly innervate the smooth muscle and gland cells of the gut. The sympathetic fibers that enter the gastrointestinal tract are postganglionic noradrenergic fibers, stimulation of which inhibits gut motility and gland secretion and contracts sphincters. Most of the noradrenergic fibers terminate either in blood vessels or on the cholinergic ganglionic cells of the intramural plexuses. These fibers alter gut motility by inhibiting acetylcholine release from the intramural nerves. Direct noradrenergic innervation of smooth muscle of the nonsphincter portion of the gut is sparse.

Salivary Glands

One exception to the generalization that the two systems work in opposition to each other is secretion by the salivary glands; both sympathetic (noradrenergic) and parasympathetic (cholinergic) activation of these glands leads to an increase in the flow of saliva. However, the nature of the saliva produced by the two systems is qualitatively different. The saliva produced by activation of the sympathetic system is a sparse, thick, mucinous secretion, whereas that produced by parasympathetic activation is a profuse, watery secretion.

THE ADRENAL MEDULLA

The cells of the adrenal medulla, called *chromaffin* cells, are homologous with sympathetic postganglionic neurons. The adrenal medulla may in fact be considered a modified sympathetic ganglion. The adrenal medulla secretes two hormones. One is norepinephrine, which is also the primary neurotransmitter of sympathetic postganglionic neurons. The other medullary hormone is epinephrine.

General activation of the sympathetic system during stress, fear, or anxiety is accompanied by increased secretion of adrenal medullary hormones, which consist primarily of epinephrine in the human. The secretory activity of the adrenal medulla is regulated by the CNS.

Some blood-borne substances of endogenous origin, such as histamine, angiotensin, and bradykinin, can directly stimulate the chromaffin cells to secrete epinephrine and norepinephrine. A variety of exogenously administered drugs, such as cholinomimetic agents and caffeine, can directly stimulate the secretion of adrenal medullary hormones. The neuronally induced secretion of medullary hormones is antagonized by ganglionic blocking agents.

TRANSMISSION OF THE NERVE IMPULSE

Microscopic studies of the structure of the terminal axons of the autonomic nerves have shown that the axons branch many times on entering the effector tissue,

forming a plexus among the innervated cells. "Swollen" areas found at intervals along the terminal axons are referred to as *varicosities* (Figs. 9.2 and 9.3). Within each varicosity are mitochondria and numerous *vesicles* containing neurotransmitters.

The vesicles are intimately involved in the release of the transmitter into the *synaptic* or *neuroeffector cleft* in response to an action potential. Following release, the transmitter must diffuse to the effector cells, where it interacts with receptors on these cells to produce a response. The distance between the varicosities and the effector cells varies considerably from tissue to tissue. Smooth muscle, cardiac muscle, and exocrine gland cells do not contain morphologically specialized regions comparable to the end plate of skeletal muscle.

In the autonomic ganglia, the varicosities in the terminal branches of the preganglionic axons come into close contact primarily with the dendrites of the ganglionic cells and make synaptic connection with them.

STEPS IN NEUROCHEMICAL TRANSMISSION

Regardless of the type of neuron under consideration, the fundamental steps in chemical transmission are the same. Each of these steps is a potential site for pharmacological intervention in the normal transmission process:

1. Synthesis of the transmitter
2. Storage of the transmitter
3. Release of the transmitter by a nerve action potential
4. Interaction of the released transmitter with receptors on the effector cell membrane and the associated change in the effector cell
5. Rapid removal of the transmitter from the vicinity of the receptors
6. Recovery of the effector cell to the state that preceded transmitter action

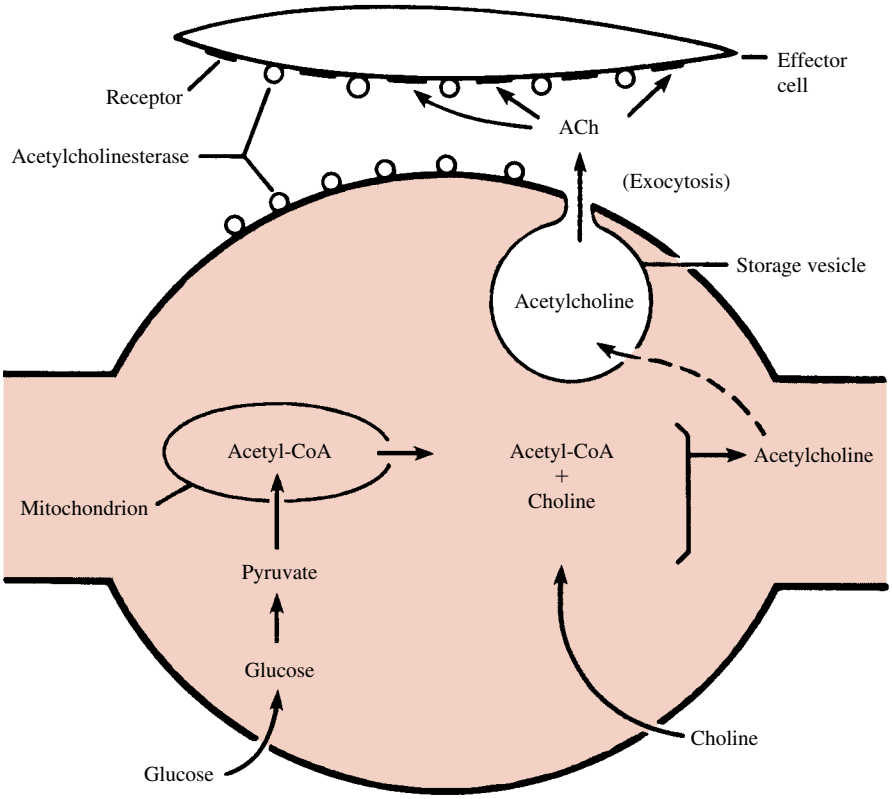

FIGURE 9.2
Varicosity showing processes of synthesis and storage of acetylcholine within a cholinergic neuron. Also shown are the release of acetylcholine (exocytosis) and the location of acetylcholinesterase, which inactivates acetylcholine.

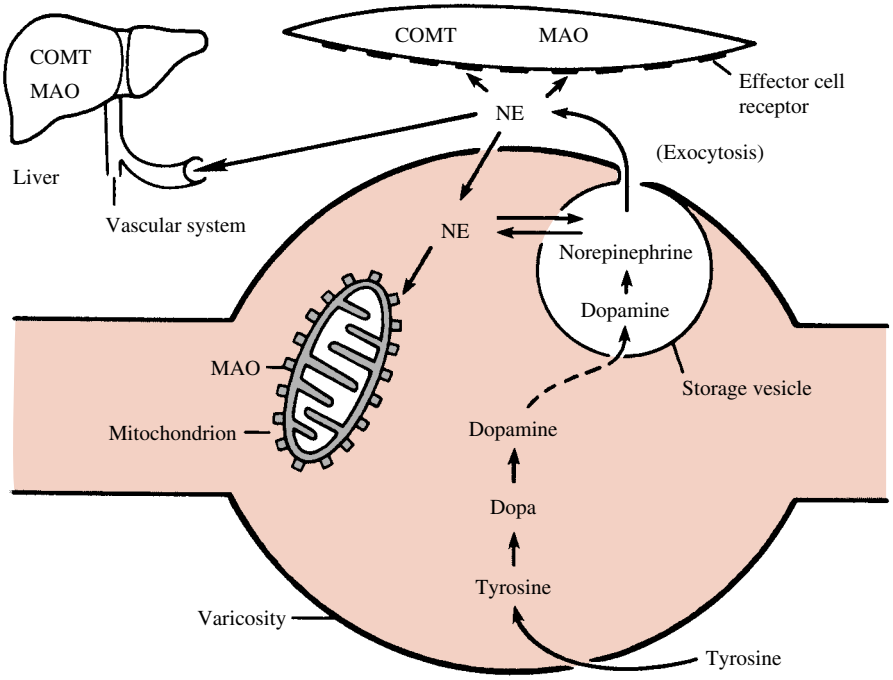

FIGURE 9.3
Varicosity of a noradrenergic neuron showing synthesis and storage of norepinephrine. Also shown is the release of norepinephrine (NE) and multiple routes for degradation. COMT, catechol-*O*-methyltransferase; MAO, monoamine oxidase.

Synthesis, Storage, Release, and Removal of Acetylcholine

The processes involved in neurochemical transmission in a cholinergic neuron are shown in Figure 9.2. The initial substrates for the synthesis of acetylcholine are *glucose* and *choline*. Glucose enters the neuron by means of facilitated transport. There is some disagreement as to whether choline enters cells by active or facilitated transport. Pyruvate derived from glucose is transported into mitochondria and converted to *acetylcoenzyme A* (*acetyl-CoA*). The acetyl-CoA is transported back into the cytosol. With the aid of the enzyme choline acetyltransferase, acetylcholine is synthesized from acetyl-CoA and choline. The acetylcholine is then transported into and stored within the storage vesicles by as yet unknown mechanisms.

Conduction of an action potential through the terminal branches of an axon causes depolarization of the varicosity membrane, resulting in the release of transmitter molecules via *exocytosis*. Once in the junctional extracellular space (biophase), acetylcholine interacts with cholinoreceptors.

A key factor in the process of exocytosis is the entry of extracellular calcium ions during the depolarization. Modification of extracellular calcium concentration or of calcium entry therefore can markedly affect neurotransmission.

The interactions between transmitters and their receptors are readily reversible, and the number of transmitter–receptor complexes formed is a direct function of the amount of transmitter in the biophase. The length of time that intact molecules of acetylcholine remain in the biophase is short because *acetylcholinesterase,* an enzyme that rapidly hydrolyzes acetylcholine, is highly concentrated on the outer surfaces of both the prejunctional (neuronal) and postjunctional (effector cell) membranes. A rapid hydrolysis of acetylcholine by the enzyme results in a lowering of the concentration of free transmitter and a rapid dissociation of the transmitter from its receptors; little or no acetylcholine escapes into the circulation. Any acetylcholine that does reach the circulation is immediately inactivated by plasma esterases.

The rapid removal of transmitter is essential to the exquisite control of neurotransmission. As a consequence of rapid removal, the magnitude and duration of effect produced by acetylcholine are directly related to the frequency of transmitter release, that is, to the frequency of action potentials generated in the neuron.

Synthesis, Storage, Release, and Removal of Norepinephrine

Transmission in noradrenergic neurons is somewhat more complex, particularly in regard to the mechanisms by which the transmitter is removed from the biophase subsequent to its release. Noradrenergic transmission is represented diagrammatically in Figure 9.3.

Synthesis of norepinephrine begins with the amino acid *tyrosine,* which enters the neuron by active transport, perhaps facilitated by a permease. In the neuronal cytosol, tyrosine is converted by the enzyme *tyrosine hydroxylase* to *dihydroxyphenylalanine* (*dopa*), which is converted to *dopamine* by the enzyme *aromatic L–amino acid decarboxylase,* sometimes termed *dopa-decarboxylase.* The dopamine is actively transported into storage vesicles, where it is converted to norepinephrine (the transmitter) by *dopamine β-hydroxylase,* an enzyme within the storage vesicle.

In noradrenergic neurons, the end product is norepinephrine. In the adrenal medulla, the synthesis is carried one step further by the enzyme *phenylethanolamine* N-*methyltransferase,* which converts norepinephrine to epinephrine. The human adrenal medulla contains approximately four times as much epinephrine as norepinephrine. The absence of this enzyme in noradrenergic neurons accounts for the absence of significant amounts of epinephrine in noradrenergic neurons. The structures of these compounds are shown in Figure 9.4.

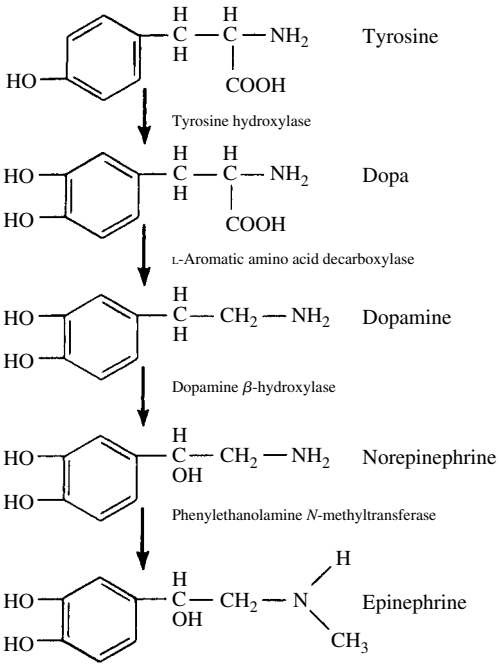

FIGURE 9.4
Steps in the synthetic pathway of epinephrine and norepinephrine.

Since the enzyme that converts dopamine to norepinephrine (dopamine β-hydroxylase) is located only within the vesicles, the transport of dopamine into the vesicle is an essential step in the synthesis of norepinephrine. This same transport system is essential for the storage of norepinephrine. There is a tendency for norepinephrine to leak from the vesicles into the cytosol. If norepinephrine remains in the cytosol, much of it will be destroyed by a mitochondrial enzyme, *monoamine oxidase* (*MAO*). However, most of the norepinephrine that leaks out of the vesicle is rapidly returned to the storage vesicles by the same transport system that carries dopamine into the storage vesicles. *It is important for a proper understanding of drug action to remember that this single transport system, called vesicular transport, is an essential element of both synthesis and storage of norepinephrine.*

Like the cholinergic transmitter, the noradrenergic transmitter is released by action potentials through exocytosis, the contents of entire vesicles being emptied into the biophase (synaptic or junctional region). Similarly, the formation of transmitter–receptor complexes is a direct function of the concentration of transmitter in the biophase and is readily reversible. In this instance, the receptors are adrenoceptors.

Three processes contribute to the removal of norepinephrine from the biophase:

1. Transport back into the noradrenergic neuron (*reuptake*), followed by either vesicular storage or by enzymatic inactivation by mitochondrial MAO. The transport of norepinephrine into the neurons is a sodium-facilitated process similar to that for choline transport.
2. Diffusion from the synapse into the circulation and ultimate enzymatic destruction in the liver and renal excretion.
3. Active transport of the released transmitter into effector cells (*extraneuronal uptake*) followed by enzymatic inactivation by catechol-*O*-methyltransferase.

The neuronal transport system is the most important mechanism for removing norepinephrine. Any norepinephrine or epinephrine in the circulation will equilibrate with the junctional extracellular fluid and thus become accessible both to the receptors and to neuronal transport. Thus, neuronal transport is also an important mechanism for limiting the effect and duration of action of norepinephrine or epinephrine, whether these are released from the adrenal medulla or are administered as drugs. *Neuronal uptake is primarily a mechanism for removing norepinephrine rather than conserving it.* Under most circumstances, synthesis of new norepinephrine is quite capable of keeping up with the needs of transmission, even in the complete absence of neuronal reuptake.

It is important to make a clear distinction between neuronal and vesicular transport. *Neuronal transport* occurs from the junctional extracellular fluid (biophase) across the cell membrane of the neuron and into the neuronal cytosol. *Vesicular transport* is from the neuronal cytosol across the membrane of the vesicle and into the vesicle. Although these two systems readily transport both norepinephrine and epinephrine, certain drugs will selectively inhibit one or the other transport system.

The second most important mechanism for removing norepinephrine from the synapse is the escape of neuronally released norepinephrine into the general circulation and its metabolism in the liver. The liver has two enzymes that perform this function: *catechol*-O-*methyltransferase* (*COMT*) and *MAO*.

COMT is a specific enzyme, accepting only catechols as substrates. A catechol is a substance with two adjacent hydroxyl groups on an unsaturated six-member ring. The end result of the action of COMT is the *O*-methylation of the meta-hydroxyl group on the catechol nucleus. Figure 9.5 illustrates the action of COMT on norepinephrine or epinephrine. This reaction reduces the biological activity of norepinephrine or epinephrine at least 100-fold.

MAO is a much less discriminating enzyme in that it will catalyze the removal of an amine group from a variety of substrates. The action of MAO on norepinephrine and epinephrine also is indicated in Figure 9.5. The list of its substrates is very large, including endogenous substances (norepinephrine, epinephrine, dopamine, tyramine, 5-hydroxy-tryptamine) and many drugs that are amines. At least in the brain, two separate forms of MAO have been described: MAO type A and MAO type B. The two types are differentiated on the basis of substrate and inhibitor specificity.

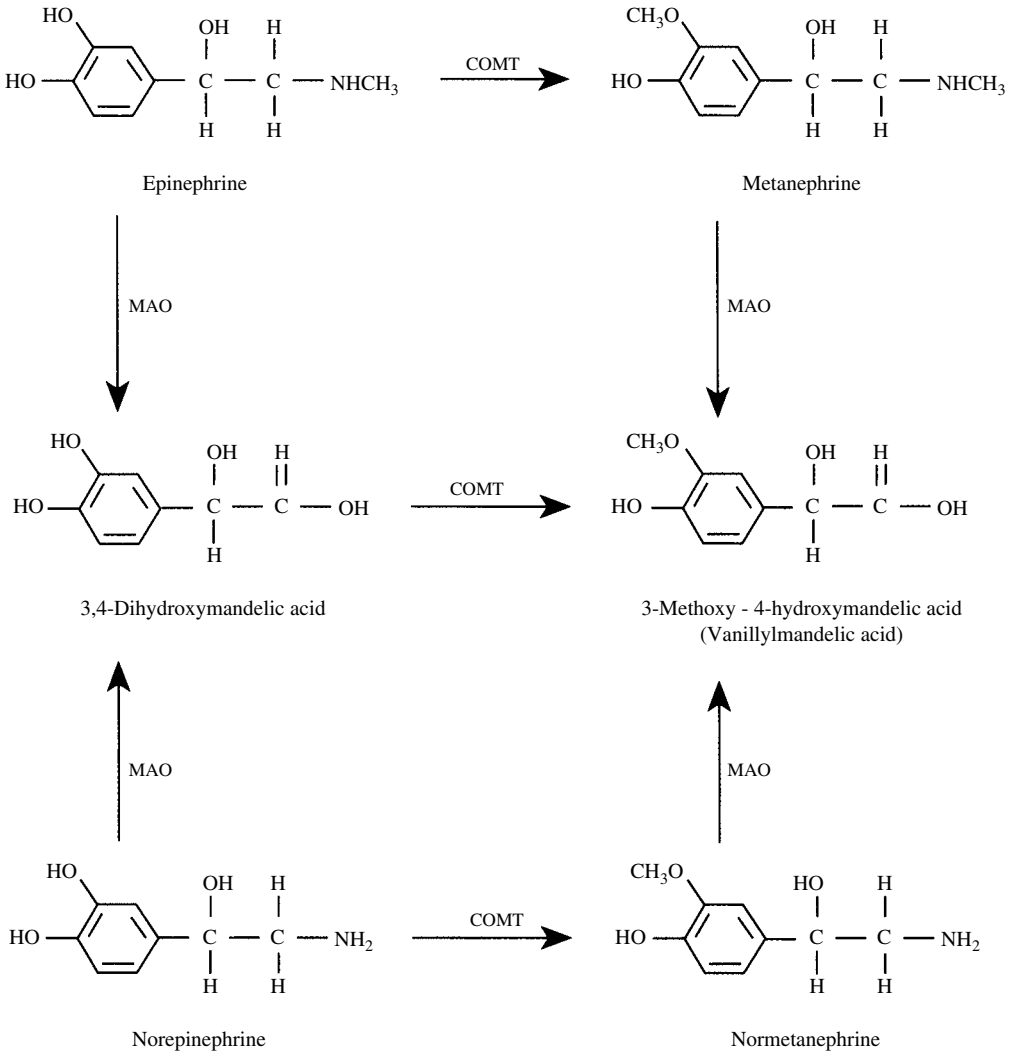

FIGURE 9.5
Primary route of metabolism of norepinephrine and epinephrine. COMT, catechol-*O*-methyltransferase; MAO, monoamine oxidase.

Although either COMT or MAO may act first on circulating norepinephrine or epinephrine, COMT is the more rapidly acting enzyme, and therefore more molecules are *O*-methylated and then deaminated than the reverse. Some norepinephrine and epinephrine appear unchanged in the urine. The larger portion, however, is metabolized and the products of metabolism excreted in the urine, often as conjugates.

Measurements of norepinephrine, epinephrine, and their metabolites in the urine constitute valuable diagnostic aids, particularly in the detection of tumors that synthesize and secrete norepinephrine and epinephrine (e.g., pheochromocytoma).

Catecholamines can be transported into effector cells (*extraneuronal uptake*). These cells generally contain both COMT and MAO. The combined processes of extraneuronal uptake and *O*-methylation are believed to be a minor but functionally significant, site of irreversible loss of catecholamines. The precise role of extraneuronal MAO in transmitter inactivation remains unknown.

RECEPTORS ON THE AUTONOMIC EFFECTOR CELLS

The receptors for acetylcholine and related drugs (*cholinoreceptors*) and for norepinephrine and related drugs (*adrenoceptors*) are different. Acetylcholine will not interact with receptors for norepinephrine, and norepinephrine will not interact with cholinoreceptors. These receptors are selective not only for their respective agonists but also for their respective antagonist drugs; that is, drugs that antagonize or block acetylcholine at cholinoreceptors will not antagonize norepinephrine at adrenoceptors and vice versa.

Cholinoceptors

The action of administered acetylcholine on effector systems innervated by parasympathetic postganglionic neurons (smooth muscle cells, cardiac muscle cells, and exocrine gland cells) resembled the actions produced by the naturally occurring plant alkaloid *muscarine.* The actions of both acetylcholine and muscarine on the visceral effectors are similar to those produced by parasympathetic nerve stimulation. Furthermore, the effects of acetylcholine, muscarine, and parasympathetic nerve stimulation on visceral effectors are antagonized by atropine, another plant alkaloid.

The administration of acetylcholine mimics the stimulatory effect of *nicotine,* the alkaloid from the tobacco plant, on autonomic ganglia and the adrenal medulla. It has become common practice to refer to the effects of acetylcholine on visceral effectors as the *muscarinic* action of acetylcholine and to its effects on the autonomic ganglia and adrenal medulla as the *nicotinic* action of acetylcholine. The respective receptors are called the muscarinic and nicotinic cholinoreceptors or the muscarinic and nicotinic receptors of acetylcholine.

The action of acetylcholine at the skeletal muscle motor end plate resembles that produced by nicotine. Thus, the cholinoreceptor on skeletal muscle is a nicotinic receptor. Based on antagonist selectivity, however, the autonomic and somatic nicotinic receptors are not pharmacologically identical (see Chapter 14).

Acetylcholine can stimulate a whole family of receptors. However, these receptors are sufficiently chemically diverse that different exogenous agonists and antagonists can distinguish among them. Great therapeutic benefit has been obtained from this diversity because it allows the development of therapeutic agents that can selectively mimic or antagonize actions of acetylcholine. Such a diversity of receptor subtypes exists for other neurotransmitters in addition to acetylcholine.

Adrenoceptors

Adrenoceptors interact not only with norepinephrine but also with the adrenal medullary hormone epinephrine and a number of chemically related drugs. However, the responses produced by the drugs in different autonomic structures differ quantitatively or qualitatively from one another.

On the basis of the observed selectivity of action among agonists and antagonists, it was proposed that two types of adrenoceptors exist. These were designated as α- and β-adrenoceptors. Subsequently, it has become necessary to classify the adrenoceptors further into α_1-, α_2-, β_1-, and β_2-receptor subtypes. Table 9.1 indicates present knowledge of the distribution of the subtypes of adrenoceptors in various tissues.

The α_1-adrenoceptors are located at postjunctional (postsynaptic) sites on tissues innervated by adrenergic neurons. α_2-Adrenoceptors having a presynaptic (i.e., neuronal) location are involved in the feedback inhibition of norepinephrine release from nerve terminals (discussed later). α_2-Receptors also can occur postjunctionally. The β_1-adrenoceptors are found chiefly in the heart and adipose tissue, while β_2-adrenoceptors are located in a number of sites, including bronchial smooth muscle and skeletal muscle blood vessels, and are associated with smooth muscle relaxation.

Activation of α_1-adrenoceptors in smooth muscle of blood vessels leads to vasoconstriction, while activation of β_2-adrenoceptors in blood vessels of skeletal muscle produces vasodilation. Activation of β_1-adrenoceptors on cardiac tissue produces an increase in the heart rate and contractile force.

Norepinephrine and epinephrine are potent α-adrenoceptor agonists, while isoproterenol, a synthetic

TABLE 9.1 Responses to Adrenergic and Cholinergic Nerve Stimulation

Organ or Tissue Function	Predominant Adrenoceptor Type	Adrenergic Response	Cholinergic Response[a]
Heart[b]			
Rate (chronotropic effect)	β_1	Increase	Decrease
Contractile force (inotropic effect)	β_1	Increase	None
Conduction velocity (dromotropic effect)	β_1	Increase	Decrease
Eye			
Pupil size	α_1	Constriction of radial muscle causing dilation (mydriasis)	Contraction of circular muscle (miosis)
Accommodation		No innervation	Contraction of ciliary muscle producing accommodation for near vision
Bronchial smooth muscle	β_2	Relaxation	Contraction
Blood vessels (arteries and arterioles)[c]			
Cutaneous	α_1	Constriction	No innervation[e]
Visceral	α_1	Constriction	No innervation[e]
Pulmonary	α_1	Constriction	No innervation[e]
Skeletal muscle	α_1, β_2	Constriction[d]	No innervation[e]
Coronary	α_1, β	Constriction, dilation[f]	No innervation[e]
Cerebral	α_1	Constriction	
Veins	α_1	Constriction	No innervation
Gastrointestinal tract (tone, motility, and secretory activity)	α_2, β_2	Decrease[g]	Increase
Sphincters	α	Contraction	Relaxation
Splenic capsule	α_1	Contraction	No innervation
Urinary bladder			
Detrusor muscle	β	Relaxation	Contraction
Trigone-sphincter muscle	α_1	Contraction	Relaxation
Uterus	α_1, β_2	Contraction-relaxation[h]	Contraction-relaxation
Glycogenolysis			
Skeletal muscle	β_2	Increase	None
Liver	α_1, β_2	Increase	None
Lipolysis	β_1	Increase	None
Renin secretion	β_1	Increase	None
Insulin secretion	α_2	Decrease	Increase

[a]Muscarinic cholinoceptors. See Chapter 12 for a discussion of subtypes.
[b]There are some β_2-receptors in the heart. The ratio of β_1 to β_2 varies with the region and the species. In the human heart, the ratio of β_1 to β_2 is about 3:2 in atria and 4:1 in ventricles.
[c]There are some α_2-receptors in some vascular smooth muscle.
[d]Low doses of epinephrine of endogenous or exogenous origin plus other β_2-receptor agonists dilate these blood vessels.
[e]Exogenously administered cholinergic drugs dilate these blood vessels.
[f]Dilation is the dominant in vivo response, owing to indirect effects.
[g]α_2-Adrenoceptors may be involved in hypersecretory responses.
[h]Responses depend on hormonal state.

adrenomimetic, is selective for β_1- and β_2-adrenoceptors. Norepinephrine and epinephrine are thus potent vasoconstrictors of vascular beds that contain predominantly α-adrenoceptors, while isoproterenol has little effect in these vessels.

Isoproterenol and epinephrine are potent β_2-adrenoceptor agonists; norepinephrine is a relatively weak β_2-adrenoceptor agonist. Isoproterenol and epinephrine produce vasodilation in skeletal muscle, but norepinephrine does not; rather it produces vasoconstriction through the α_1-adrenoceptors. Isoproterenol, epinephrine, and norepinephrine are potent β_1-adrenoceptor agonists; thus, all three can stimulate the heart (Table 9.1).

The existence of a β_3-adrenoceptor has recently been demonstrated in human adipose tissue along with the β_1-adrenoceptor. This observation raises the possibility that eventually therapeutic drugs may selectively alter lipid metabolism and therefore provide therapeutic management of obesity. The β_3-receptor and the recently identified subtypes within the α_1- and α_2-receptor groups (α_{1A}, α_{1B}, etc.) also have not been included in the

table, since as yet few therapeutic drugs distinguish among these further subtypes. One exception is tamsulosin, an antagonist with some selectivity for α_{1A}-receptors in the urinary tract.

Presynaptic Receptors

Presynaptic or *prejunctional receptors* are located on the presynaptic nerve endings and function to control the amount of transmitter released per nerve impulse and in some instances to affect the rate of transmitter synthesis through some as yet undetermined feedback mechanism. For instance, during repetitive nerve stimulation, when the concentration of transmitter released into the synaptic or junctional cleft is relatively high, the released transmitter may activate presynaptic receptors and thereby reduce the further release of transmitter. Such an action may prevent excessive and prolonged stimulation of the postsynaptic cell. In this case, the activation of the presynaptic receptor would be part of a *negative feedback mechanism.*

The presynaptic receptors may have pharmacological significance, since several drugs may act in part either by preventing the transmitter from reaching the presynaptic receptor, thus causing excessive transmitter release, or by directly stimulating presynaptic receptors and thereby diminishing the amount of transmitter released per impulse.

The inhibitory presynaptic α-adrenoceptors found on noradrenergic neurons are of the α_2-subtype. Adrenoceptors of the β_2 subclass also occur presynaptically, and activation of these receptors leads to enhanced norepinephrine release. The physiological and pharmacological importance of these presynaptic β_2-receptors is less certain than it is for presynaptic α_2-receptors.

Presynaptic receptors for nonadrenomimetic substances (e.g., acetylcholine, adenosine) also have been found on the sympathetic presynaptic nerve ending. Their importance and role in the modulation of neurotransmission have not been definitively established.

PHARMACOLOGICAL INTERVENTION IN NEUROTRANSMISSION

The drugs listed in Table 9.2 affect specific steps in cholinergic or adrenergic transmission. These and many other drugs that alter transmission are discussed in subsequent chapters.

TABLE 9.2 Drugs that interfere with Specific Steps in Chemical Transmission

Transmission Step	Adrenergic Nerves	Cholinergic Nerves
Synthesis of transmitter	α-Methyldopa	Hemicholinium
Storage of transmitter	Reserpine	None known
Release of transmitter	Guanethidine	Botulinum toxin
Combination of transmitter with receptor	Prazosin (α-receptors)	Atropine (muscarinic receptors)
	Propranolol (β-receptors)	*d*-Tubocurarine (nicotinic receptors)
Destruction or removal of transmitter from site of action	Tolcapone (COMT inhibitor)	Physostigmine (cholinesterase inhibitor)
	Phenelzine (MAO inhibitor)	
	Tricyclic antidepressants (inhibit neuronal transport)	
Recovery of postsynaptic cell from the effects of the transmitter	None known	Succinylcholine

COMT, catechol-*O*-methyltransferase; MAO, monoamine oxidase.

Study Questions

1. All of the following types of cells are innervated by the autonomic nervous system EXCEPT:
(A) Smooth muscle of blood vessels
(B) Skeletal muscle
(C) Sinoatrial node
(D) Salivary glands
(E) Intestinal smooth muscle

2. All of the following structures have a significant cholinergic innervation EXCEPT:
(A) Ventricular wall
(B) Sinoatrial node
(C) Atrioventricular node
(D) Bladder
(E) Ileum

3. The radial smooth muscle of the iris is innervated by:
   (A) Primarily sympathetic noradrenergic neurons
   (B) Primarily sympathetic cholinergic neurons
   (C) Primarily parasympathetic noradrenergic neurons
   (D) Primarily parasympathetic cholinergic neurons
   (E) Equally by sympathetic and parasympathetic neurons
4. The receptors on the skeletal muscle end plate respond to:
   (A) Acetylcholine and muscarine
   (B) Acetylcholine and nicotine
   (C) Acetylcholine, muscarine, and nicotine
   (D) Only muscarine of the three choices in C
   (E) Only nicotine of the three choices in C
5. α_1-Adrenoceptors are prominently involved in which one of the following?
   (A) Cardiac acceleration
   (B) Intestinal relaxation
   (C) Cardiac contractility
   (D) Presynaptic inhibition
   (E) Vasoconstriction
6. Smooth muscle relaxation is most associated with which one of the following adrenoceptors?
   (A) β_1
   (B) β_2
   (C) β_3
   (D) α_1
   (E) α_2

ANSWERS

1. **B.** Skeletal muscle is innervated by the somatic nervous system. All other choices are tissues that are innervated by the autonomic nervous system.
2. **A.** Cholinergic fibers do not innervate the ventricular muscles, although there is significant cholinergic innervation to the SA node (B) and the AV node (C). The gastrointestinal tract, including the ileum (E), is extensively innervated by cholinergic fibers, as is the bladder (D).
3. **A.** Stimulation of the sympathetic noradrenergic neurons to the iris causes contraction of the radial smooth muscle and dilation of the pupil (mydriasis).
4. **B.** The receptor on skeletal muscle end plate is characterized as a nicotinic receptor. It responds to both nicotine and to acetylcholine. It does not respond to muscarine; that is, it is not a muscarinic receptor.
5. **E.** α_1-Receptors are prominent in smooth muscle of blood vessels; activation of these receptors leads to vasoconstriction. Cardiac acceleration (A) and cardiac contraction (C) are primarily due to β_1-receptor stimulation. Intestinal relaxation occurs as a result of stimulation of α_1- and β_1-receptor stimulation.
6. **B.** Smooth muscle relaxation is primarily under the influence of the sympathetic nervous system. This control is primarily through β_2-receptors. β_1-Receptors are found chiefly in the heart and adipose tissue. α_1-Receptors are at postjuctional sites on tissues innervated by adrenergic neurons. α_2-Receptors are usually presynaptic, while β_3-adrenoceptors appear to be primarily in adipose tissue.

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